

CLAIMS

What is claimed is:

1. A method for identifying desirable protein backbone configurations comprising:
generating backbone protein configurations using a set of dihedral angle pairs;
normalizing the total surface exposure of each remaining configuration;
generating a random set of sequences of hydrophobicities with uniform weight on the space of allowed sequences;
determining, for each randomly generated sequence, which of the remaining configurations is the ground state, and;
recording a ground-state configuration for each sequence wherein the desirable configurations are those containing the most sequences with that configuration as their ground state.
2. A method for identifying desirable protein backbone configurations as in claim 1 wherein:
one pair of dihedral angle pairs corresponds to an alpha helix and one pair of dihedral angle pairs corresponds to a beta strand.
3. A method for identifying desirable protein backbone configurations as in claim 1 wherein:
two sets of dihedral angles correspond to an alpha helix and one set of dihedral angle pairs corresponds to a beta strand.
4. A method for identifying desirable protein backbone configurations as in claim 3 wherein:
additional dihedral angles fall within regions of high frequency in a Ramachandran plot.
5. A method for identifying desirable protein backbone configurations as in claim 4 wherein:

the probability of choosing a particular pair of dihedral angles depends on the preceding pairs of dihedral angles along the backbone.

- 5 6. A method for identifying desirable protein backbone configurations as in claim 5 further comprising:

eliminating self-intersecting configurations.

7. A method for identifying desirable protein backbone configurations as in claim 6 further comprising:

10 eliminating non-compact configurations.

8. A method for identifying desirable protein backbone configurations as in claim 7 further comprising:

clustering configurations sufficiently similar in the three dimensional trajectory followed by their backbones and treating all configurations within a cluster as variants of a single configuration, and;

summing, for all configurations in a cluster, the number of sequences with that configuration as their group state such that the sum is considered the designability of the cluster.

9. A method for identifying desirable protein backbone configurations as in claim 8 further comprising:

eliminating configurations with low Variances.

- 25 10. A method for identifying desirable protein backbone configurations as in claim 1 wherein:

the set of dihedral angle pairs is a set of strings of dihedral angle pairs.

- 30 11. A method for identifying desirable protein backbone configurations as in claim 10 wherein:

the strings of angles are weighted according to their frequency of appearance in natural proteins and infrequent strings are eliminated.

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12. A method for identifying desirable protein backbone configurations as in claim 1 wherein:
normalizing is accomplished by dividing the surface exposure of each amino acid in a given configuration by the total surface exposure of that configuration.
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13. A method for identifying desirable protein backbone configurations as in claim 1 further comprising:
eliminating configurations with low Variance.
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14. A method for identifying desirable protein backbone configurations as in claim 1 further comprising:
eliminating self-intersecting configurations.
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15. A method for identifying desirable protein backbone configurations as in claim 14 further comprising:
eliminating non-compact configurations.
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16. A method for identifying desirable protein backbone configurations as in claim 1 further comprising:
eliminating non-compact configurations.
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17. A method for identifying desirable protein backbone configurations as in claim 1 further comprising:
eliminating configurations with low Variance.
18. A method for identifying desirable protein backbone configurations as in claim 1 further comprising:

eliminating all configurations that are not favorable for forming a large number of hydrogen bonds after eliminating non-compact configurations.

- 5 19. A method for identifying desirable protein backbone configurations as in claim 1 further comprising:

clustering configurations sufficiently similar in the three dimensional trajectory followed by their backbones and treating all configurations within a cluster as variants of a single configuration, and;

10 summing, for all configurations in a cluster, the number of sequences with that configuration as their ground state such that the sum is considered the designability of the cluster.

20. A method for identifying desirable protein backbone configurations as in claim 19 wherein:

clustering is accomplished by totaling the root-mean-square distance between every pair of configurations and defining a configuration as a member of a cluster if it lies within a root-mean-square distance λ of any member of the cluster.

21. A method for identifying desirable protein backbone configurations as in claim 20 wherein:

λ is 0.4 Å per amino acid.

22. A method for designing proteins comprising:

generating backbone protein configurations using a set of dihedral angle pairs;

25 eliminating self-intersecting configurations;

normalizing the total surface exposure of each remaining configuration;

generating a random set of sequences of hydrophobicities with uniform weight on the space of allowed sequences for each remaining configuration;

30 determining, for each randomly generated sequence, which of the remaining configurations is the ground state;

recording the ground-state configuration for each sequence wherein desirable configurations are those containing the most sequences with that configuration as their ground state, and;

synthesizing sequences of amino acids for the desirable configurations.

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23. A method for designing proteins as in claim 22 wherein:
one set of dihedral angle pairs corresponds to an alpha helix and one set of dihedral angles corresponds to a beta strand.

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24. A method for designing proteins as in claim 22 wherein:
two sets of dihedral angles correspond to an alpha helix and one set of dihedral angle pairs corresponds to a beta strand.

25. A method for designing proteins as in claim 24 wherein:
additional dihedral angle pairs fall within regions of high frequency in a Ramachandran plot.

26. A method for designing proteins as in claim 25 wherein:
the probability of choosing a particular pair of dihedral angles depends on the preceeding pairs of dihedral angles along the backbone.

27. A method for designing proteins as in claim 26 further comprising:
eliminating self-intersecting configurations.

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28. A method for designing proteins as in claim 27 further comprising:
eliminating non-compact configurations.

29. A method for designing proteins as in claim 28 further comprising:

clustering configurations sufficiently similar in the three dimensional trajectory followed by their backbones and treating all configurations within a cluster as variants of a single configuration, and;

summing, for all configurations in a cluster, the number of sequences with that configuration as their ground state such that the sum is considered the designability of the cluster.

30. A method for designing proteins as in claim 29 further comprising:
recording the Variance of each configuration, ranking the configurations from
highest Variance to lowest, and
designing proteins starting with the configurations having the highest Variance.
31. A method for designing proteins as in claim 22 wherein:
the set of dihedral angles is a set of strings of dihedral angles.
32. A method for designing proteins as in claim 31 wherein:
the strings of angles are weighted according to their frequency of appearance in
natural proteins and infrequent strings are eliminated.
33. A method for designing proteins as in claim 22 wherein:
normalizing is accomplished by dividing the surface exposure of each amino acid
in a given configuration by the total surface exposure of that configuration.
34. A method for designing proteins as in claim 22 further comprising:
recording the Variance of each configuration, ranking the configurations from
highest Variance to lowest, and
designing proteins starting with the configurations having the highest Variance.
35. A method for designing proteins as in claim 22 further comprising:
eliminating non-compact configurations after self-intersecting configurations are
eliminated.

36. A method for designing proteins as in claim 35 further comprising:

clustering configurations sufficiently similar in the three dimensional trajectory followed by their backbones and treating all configurations within a cluster as variants of a single configuration, and;

summing, for all configurations in a cluster, the number of sequences with that configuration as their ground state such that the sum is considered the designability of the cluster.

37. A method for designing proteins as in claim 22 further comprising:

eliminating all configurations that are not favorable for forming hydrogen bonds after eliminating non-compact configurations.

38. A method for designing proteins as in claim 22 further comprising:

clustering configurations sufficiently similar in the three dimensional trajectory followed by their backbones and treating all configurations within a cluster as variants of a single configuration, and;

summing, for all configurations in a cluster, the number of sequences with that configuration as their ground state such that the sum is considered the designability of the cluster.

39. A method for designing proteins as in claim 38 wherein:

clustering is accomplished by totaling the root-mean-square distance between every pair of configurations and defining a configuration as a member of a cluster if it lies within a root-mean-square distance λ of any member of the cluster.

40. A method for designing proteins as in claim 39 wherein:

λ is 0.4 Angstroms per amino acid.

41. A method for analyzing the designability of protein backbone configurations to determine if the number of sequences each configuration has in its ground state is larger than a predetermined number comprising:

generating backbone protein configurations using a set of dihedral angle pairs;

eliminating self-intersecting configurations;

normalizing the total surface exposure of each remaining configuration;

generating a random set of sequences of hydrophobicities with uniform weight on the space of allowed sequences;

determining, for each randomly generated sequence, which of the remaining configurations is the ground state;

recording a ground-state configuration for each sequence wherein the desirable configurations are those containing the most sequences with that configuration as their ground state, and;

comparing how many sequences each configuration has in its ground-state with the predetermined number whereby configurations with larger numbers are highly designable.

42. A method for analyzing the designability of protein backbone configurations as in claim 41 wherein:

normalizing is accomplished by dividing the surface exposure of each amino acid in a given configuration by the total surface exposure of that configuration.

43. A method for analyzing the designability of protein backbone configurations as in claim 41 wherein:

one set of dihedral angle pairs corresponds to an alpha helix and one set of dihedral angle pairs corresponds to a beta strand.

44. A method for analyzing the designability of protein backbone configurations as in claim 41 wherein:

two sets of dihedral angle pairs correspond to an alpha helix and one set of dihedral angle pairs corresponds to a beta strand.

45. A method for analyzing the designability of protein backbone configurations as in claim 44 wherein:

additional dihedral angles fall within regions of high frequency in a
Ramachandran plot.

46. A method for analyzing the designability of protein backbone configurations as in claim 45 wherein:

the probability of choosing a particular pair of dihedral angles depends on the
preceeding pairs of dihedral angles along the backbone.

47. A method for analyzing the designability of protein backbone configurations as in claim 46 further comprising:

eliminating non-compact configurations after self-intersecting configurations are
eliminated.

48. A method for analyzing the designability of protein backbone configurations as in claim 47 further comprising:

recording the Variance of each configuration, ranking the configurations from
highest Variance to lowest, and
designing proteins starting with the configurations having the highest Variance.

49. A method for analyzing the designability of protein backbone configurations as in claim 48 further comprising:

clustering configurations sufficiently similar in the three dimensional trajectory
followed by their backbones and treating all configurations within a cluster as variants of
a single configuration, and;

summing, for all configurations in a cluster, the number of sequences with that
configuration as their ground state such that the sum is considered the designability of the
cluster.

50. A method for analyzing the designability of protein backbone configurations as in claim 41 wherein:

the set of dihedral angle pairs is a set of strings of dihedral angle pairs.

5 51. A method for analyzing the designability of protein backbone configurations as in claim 49 wherein:

the strings of angles are weighted according to their frequency of appearance in natural proteins and infrequent strings are eliminated.

10 52. A method for analyzing the designability of protein backbone configurations as in claim 41 wherein:

the probability of choosing a particular pair of dihedral angles depends on the preceeding pairs of dihedral angles along the backbone.

15 53. A method for analyzing the designability of protein backbone configurations as in claim 41 further comprising:

recording the Variance of each configuration, ranking the configurations from highest Variance to lowest, and
designing proteins starting with the configurations having the highest Variance.

20 54. A method for analyzing the designability of protein backbone configurations as in claim 41 further comprising:

eliminating all configurations that are not favorable for forming a large number of hydrogen bonds after eliminating non-compact configurations.

25 55. A method for analyzing the designability of protein backbone configurations as in claim 41 further comprising:

clustering configurations sufficiently similar in the three dimensional trajectory followed by their backbones and treating all configurations within a cluster as variants of a single configuration, and;

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